Remarks

On page 2 of the instant Office Action, the Examiner submits that "embodiments of the invention such as use of a compound to treat CR ... and specific genes that have been found to be differentially modulated listed in Tables 1-3 ... are not supported in U.S. Provisional Patent Application No. 60/405,225." Applicants respectfully direct the Examiner's attention to page 5, (fourth full paragraph) of U.S. Provisional Application No. 60/405,225, which provides for methods of preventing, inhibiting, reducing or treating CR using a compound that modulates the synthesis, expression or activity of one or more genes or gene products as disclosed in Tables 1, 2 or 3. Applicants also respectfully direct the Examiner's attention to original Table 3, which is present at page 25 of U.S. Provisional Application No. 60/405,225. Table 3 in the U.S. Provisional Application No. 60/405,225 sets forth the GenBank® Accession Numbers and gene names for ten exemplary nucleic acid sequences for use in the presently claimed methods. These nucleic acid sequences are additionally discussed at, e.g., pages 5-6 of U.S. Provisional Application No. 60/405,225. Thus, Applicants respectfully submit that all claims are entitled to the filing date of the provisional application, i.e., August 22, 2002.

Rejections Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claim 7 as indefinite under 35 U.S.C. §112. Solely in order to expedite prosecution, Applicants have cancelled claim 7, rendering the instant indefiniteness-based rejection moot.

Rejections Under 35 U.S.C. §112, First Paragraph

I. Enablement

The *MPEP* outlines a two-stage inquiry for rejecting a claim as overly broad. The first stage requires determining precisely how broad a claim is with respect to the disclosure. *MPEP* § 2164.08. The second stage of the inquiry requires determining whether the specification teaches one of ordinary skill in the art how to make and use the scope of what is claimed without

undue experimentation. *Id*; *see also, In re Moore*, 439 F.2d 1232, 1236 (C.C.P.A. 1971) (stating that an enablement inquiry asks "whether the scope of enablement provided to one of ordinary skill in the art by the disclosure is such as to be commensurate with the scope of protection sought by the claims.").

A. *The Scope of the Claims*

The scope of a claim must be commensurate with the disclosures in the specification. *See In re Wright*, 999 F.2d 1557 (Fed. Cir. 1993); *see In re Moore*, 439 F.2d 1232. More precisely, the scope of enablement must bear a "reasonable correlation" to the scope of the claims. *In re Fisher*, 427 F.2d 833, 839 (C.C.P.A. 1970). In determining inventive scope, the claims are to be "given [the] broadest reasonable interpretation consistent with the specification." *In re Hyatt*, 211 F.3d 1367, 1372 (Fed. Cir 2000). Thus, an interpretation is only "reasonable" when it is formulated in light of the disclosure.

The Examiner has rejected claims 2, 6, 8 and 9 as lacking enablement under 35 U.S.C. §112. In an effort to expedite prosecution and allowance of the pending claims in the present application, Applicants have amended all claims to recite that the transplanted subject must be a kidney transplanted subject. In addition, all claims now require the mRNAs, proteins, genes or gene products that are measured/compared and/or regulated to correspond to, be encoded by, or actually be the nucleic acid sequences set forth in Table 3. The disclosed study identifies the intra-individual changes of gene expression profiles (rather than single genes) during the time after transplantation and until the last normal biopsy before CR was diagnosed (i.e., concurrent changes in gene expression patterns for a number of genes between baseline and the last biopsy before occurrence (or non-occurrence) of CR). Thus, the claims have been amended to reflect that it is the change in expression pattern of the nucleic acid sequences in Table 3 that are useful to predict later occurrence of CR. Accordingly, the scope of all pending claims in relation to the type of transplanted subject, and the mRNA, protein, gene or gene product has been significantly narrowed. For at least this reason, Applicants respectfully request withdrawal of the outstanding enablement-based rejection.

Applicants have also limited the "compound" of claim 4 to a "CR-inhibiting agent". The Examiner is of the opinion that the genus of CR-inhibiting agents recited in claim 4 is a very large genus because such agents may be small molecules, antibodies or drug compounds. *Office Action* at page 10. Applicants with to emphasize that not all small molecules, antibodies and drug compounds would fall within the scope of the amended claims. The agents of claim 4 are described by membership in a two narrow functional classes – 1) they must be capable of modulating the synthesis, expression or activity of the nucleic acid sequences in Table 3; and 2) they must be a CR-inhibiting agent. Therefore, Applicants respectfully submit that the Examiner's interpretation of the claim breadth is not reasonable in light of the disclosure, and especially in light of the present amendments. For at least this reason, Applicants respectfully request withdrawal of the outstanding enablement-based rejection.

B. *The Disclosure*

To satisfy §112, an applicant must disclose an amount sufficient to allow one skilled in the art to practice the invention without undue experimentation. *See In re Buchner*, 929 F.2d 660 (Fed. Cir. 1991). However, that some experimentation (or even extensive experimentation) is required to practice a claimed invention does not necessarily invalidate a claim under §112. *See In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988) (stating "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed."). Therefore, "[e]nablement is not precluded by the necessity for some experimentation ... . 'The key word is 'undue,' not 'experimentation.'" *In re Wands*, 858 F.2d at 736-7 (*quoting*, *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A 1974)). Accordingly, trial-and-error may be acceptable and will not render a claim invalid if the experimentation is routine or the specification provides a reasonable amount of guidance. *See In re Vaeck*, 947 F.2d 488, 495 (Fed. Cir. 1991) ("That some experimentation may be required is not fatal... .")

An applicant may claim an invention generically if it is described sufficiently to meet the requirements of § 112, ¶1. *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991). To support a genus claim, an applicant must identify a sufficient number of species to represent the claimed genus. *Id.* If experimentation is required to make the invention, the

applicant must "provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d at 737. However, an applicant may omit that which is well known or routine in the art. *See Hybritech, Inc. v. Monoclocal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986) (stating that "a patent need not teach, and preferably omits, what is well known in the art."); *see In re Wands*, 858 F.2d at 736-7; MPEP § 2164.05(b) at 2100-185.

In light of the requirements set forth by the courts, Applicants have satisfied the enablement requirement of 35 U.S.C. § 112 by disclosing a sufficient number of nucleic acid sequences useful for early diagnosis of CR in a kidney transplanted subject, nucleic acid sequences that may be used for monitoring CR in a kidney transplanted subject, and nucleic acid sequences that, when modulated, result in prevention, inhibition or reduction of CR. Applicants have provided over sixty nucleic acid sequences that are differentially regulated in subjects undergoing CR in comparison to subjects that do not suffer from CR (see Tables 1 and 2). Moreover, Applicants have provided significant guidance to enable one of ordinary skill to make and use the instant claims by identifying and providing the exemplary nucleic acid sequences in Table 3, to which all amended claims now refer. Thus, while Applicants have disclosed more than 60 useful nucleic acid sequences for CR diagnosis and monitoring, and which are reasonably expected to provide prevention, inhibition or reduction of CR when modulated, the claims now recite measuring modulation of the ten exemplary nucleic acid sequences (or, e.g., expressed protein from such genes) set forth in Table 3.

Regardless of the Examiner's assertion on pages 5-7 of the instant Office Action that Damrauer et al. provides for unpredictability in the art [1]Applicants have set forth solid data

[1] The Examiner argues that Damrauer suggests that some genes with altered expression may have gene profiles that not relevant to a biological question, and that perhaps these genes are differentially regulated due to decreased kidney disease. *Office Action* at page 7. However, in the instant application the biopsies used to define the differential expression patterns were all obtained before CR occurred, and therefore before renal function deteriorated. Therefore, one can reasonably exclude that the changes in patterns in the instant application are purely a reflection of declining renal function.

The Examiner has also suggested that the differential regulation of the listed genes may result from a response to transplant-related medication. The two populations (those who progressed to CR and those who did not) could possibly have responded differently to medication, which may have contributed to the differential change in pattern. If so, this would identify a factor contributing to CR. However, for whatever reason, and by whatever mechanism, the expression profile of the genes in Tables 1 and 2, especially the expression profile of the genes in Table 3, are, indeed, *predictive* of decreased occurrences of CR in kidney transplant patients. Indeed, the change in a gene expression profile of the genes in Table

showing that in a parallel group transplantation study, when comparing subjects that do not exhibit CR following kidney transplant to those subjects that do exhibit CR following kidney transplant, the expression profile of certain nucleic acid sequences, especially those shown in Table 3, highly correlates to CR (see, e.g., the p values of the nucleic acid sequences set forth in Tables 1 and 2). In fact, "the occurrence/non occurrence of chronic rejection was predicted in 15 out of these 17 patients (>88%)". *Specification* at page 18. Thus, Applicants submit that instant specification contradicts any unpredictability set forth by Damrauer.

Regarding the Examiner's concern over the breadth of inhibitory agents recited in the claims, Applicants are not required to disclose a list of CR-inhibitory agents for use in the pending claims. Applicants may omit what is well-known, e.g., the well-known use of immunosuppressants, rennin inhibitors and ACE inhibitors for treating chronic rejection. Alternatively, Applicants may simply provide reasonable guidance to enable others to obtain such CR-inhibitory compounds (e.g., CR-inhibitory compounds that regulate the genes set forth in Table 3). Applicants have provided exemplary genes differentially regulated in subjects suffering from CR following kidney transplantation that one may use to identify a particular CR-inhibitory agent. Moreover, Applicants have identified several well-known methods that may be used to identify compounds that induce changes in gene expression (Northern hybridization, hybridization methods, arrays, RT-PCR, etc.). *Specification* at page 3. There is also extensive objective evidence that one of ordinary skill would be able to narrow a genus of compounds to a finite number of CR-inhibitory candidates for use in the pending method claims based on the specification and the level of knowledge in the art. Those of ordinary skill possess the requisite knowledge to formulate a manageable list of candidate compounds that may be screened for CR-inhibition based on the disclosure. There are in fact numerous, well-known, small-molecule databases available to one of skill in the art to help screen for CR-inhibitors using the above-mentioned assays and differentially regulated genes. Furthermore, the design of CR-inhibitors

---

3 may offer a possibility to reflect a multifactorial disease process. Applicants are not required to know how or why their invention works, only that that their invention does work. *Fromson v. Advance Offset Plate, Inc.* 720 F.2d 1565 (Fed. Cir. 1983); *Newman v. Quigg*, 877 F.2d 1575, 1581-82 (Fed. Cir. 1989) (Stating "it is not a requirement of patentability that the inventor correctly set forth, or even know how or why the invention works.").

that are expected to directly regulate the expression of the differentially regulated genes described in the instant specification (e.g., antisense RNA or siRNA) is well established in the art. *See* Reynolds et al. (2004) *Nat. Biotechnol.* 22:326-30 (provided herewith as a courtesy copy). By disclosing CR-differentially regulated genes as staring points, and describing assays that one may use to monitor changes in the expression of these genes in, e.g., kidney transplant biopsy samples, Applicants have provided the "reasonable guidance" required to enable one of ordinary skill to identify CR-inhibitory agents, and thus to make the invention that is the subject of the claims. *In re Wands*, 858 F.2d at 737. As a result, screening for regulators of the nucleic acid sequences set forth in Table 3 that are CR-inhibiting agents becomes simple, routine trial and error.

For at least the reasons set forth above, Applicants respectfully submit that the instantly pending claims are enabled, and respectfully request withdrawal of all outstanding enablement-based rejections.

II. Written Description

The Examiner has rejected claims 2, 6, 8 and 9 as lacking an adequate written description under 35 U.S.C. §112. For the following reasons, that rejection is respectfully traversed.

The purpose of the § 112 written description requirement is to ensure that an applicant possesses the claimed invention at the time of filing. *See Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 323 F.3d 956 (Fed. Cir. 2002). For chemical compounds, an applicant must disclose sufficient identifying characteristics so one of skill can "visualize or recognize the identity" of the invention. *Regents of the University of California v. Eli Lilly, Co.,* 119 F.3d 1559, 1568 (Fed. Cir. 1997). For a generic claim, the "specification [must] describe a sufficient number of species within the very broad genus to indicate that the inventors had made a generic invention, i.e., that they had possession of the breadth of the genus, as opposed to merely one or two such species." *Enzo* at 967.

Applicants have amended the claims to recite the nucleic acid sequences set forth in Table 3. Applicants believe that this answers a significant portion of the Examiner's written

description-based rejections. However, the Examiner has also based the written description rejection on the premise that specification discloses only general embodiments of the CR-inhibitory agent recited in claim 4 without providing any common attributes of such agents. *Office Action* at p. 13. As stated above (see Enablement section), Applicants believe the genus of CR-inhibitory agents is narrower in scope than defined by the Examiner; therefore, fewer characteristics need be disclosed. These compounds are described by membership in a two functional classes, with two common attributes – 1) the agents used in the claim 4 must be capable of modulating the synthesis, expression or activity of the nucleic acid sequences in Table 3; and 2) the agent must be a CR-inhibiting agent.

To satisfy the written description requirement, Applicants need only "reasonably convey" sufficient characteristics so that a skilled artisan can "visualize or recognize the identity" of the invention. *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985); *Regents*, 119 F.3d at 1568. To support the pending method claims, Applicants have: 1) described several general categories or classes of molecules (small molecules, antibody or other therapeutic agent); and 2) disclosed nucleic acid sequences and assays useful to identify specific CR-inhibitory agents. Applicants have reasonably conveyed to a skilled artisan that they are in possession of claims reciting "CR-inhibitory agent". That the disclosure contemplates disparate CR-inhibitory agents is not relevant to a written description analysis, because written description requires a showing of possession rather than enabling extrapolation. *See In re Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989).

Rejections Under 35 U.S.C. §102

The Examiner has rejected pending claims 1, 3-4 and 10-11 as anticipated under 35 U.S.C. §102. Applicants note that the Examiner did not reject as anticipated previously-pending claim 7, which referred to the nucleic acid sequences identified in the instant application as correlating to CR. Thus, Applicants respectfully submit that the amendments to the claims, i.e., the addition of the sequences corresponding to the exemplary nucleic acid sequences of Table

3, overcome all outstanding novelty-based rejections. For at least this reason, Applicants respectfully request withdrawal of the outstanding obviousness-based rejections of pending claims 1, 3-4 and 10-11.

Rejections Under 35 U.S.C. §103

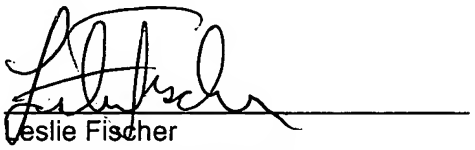
The Examiner has rejected pending claims 2, 8 and 9 as obvious under 35 U.S.C. §103. Applicants note that the Examiner did not reject as obvious previously-pending claim 7, which referred to the nucleic acid sequences identified in the instant application as correlating to CR. Thus, Applicants respectfully submit that the amendments to the claims, i.e., the addition of the sequences corresponding to the exemplary nucleic acid sequences of Table 3, overcome all outstanding obviousness-based rejections. For at least this reason, Applicants respectfully request withdrawal of the outstanding obviousness-based rejections of pending claims 2, 8 and 9.

CONCLUSION

In view of the above amendments and remarks, Applicants submit that all of the Examiner's concerns have been answered and overcome, and that the presently claimed invention satisfies 35 U.S.C. §112 and is neither disclosed nor suggested by any art of record. Accordingly, reconsideration and allowance of all claims are earnestly solicited.

Applicants' undersigned attorney may be reached by telephone at (862) 778-9308. All correspondence should continue to be directed to our below-listed address.

Respectfully submitted,



Leslie Fischer
Attorney for Applicants
Reg. No. 58,393

Novartis Pharmaceuticals Corp.
Patents Pharma
One Health Plaza, Building 104
East Hanover, NJ 07936-1080
(862) 778-9308

Date: April 24, 2008